Michigan Department of Community Health

MDCH

Interpretation of Newborn Hemoglobin Screening Results

There are nearly 600 human hemoglobin variants. The vast majority were discovered during population surveys and are not associated with clinical manifestations.

The purpose of newborn hemoglobin screening is to detect sickle cell disease. The most common types of sickle cell disease are sickle cell anemia (SS), sickle cell – hemoglobin C disease (SC) and sickle thalassemia (S-beta-thal). These conditions render infants susceptible to overwhelming pneumococcal infection and acute splenic sequestration. These life-threatening complications may occur prior to other less severe complications that would lead to the routine diagnosis and institution of prevention measures. Infection and death can be virtually eliminated by continuous penicillin prophylaxis from age 3 months to 6 years.

The methodology for initial newborn screening (high performance liquid chromatography and isoelectric focusing) in the newborn period can make a definitive diagnosis of sickle cell – hemoglobin C disease for which the newborn test results would be FSC. However, only a presumptive diagnosis of sickle cell anemia can be made. This is because the pattern typical of sickle cell anemia (FS) is also found in:

- Sickle cell – beta thalassemia zero which is clinically similar to sickle cell anemia
- Sickle beta thalassemia plus which is generally a mild form of sickle cell disease characterized by the presence of a small amount of adult hemoglobin which can be masked by the large amount of fetal hemoglobin present in the normal newborn
- Sickle cell with hereditary persistence of fetal hemoglobin (HPFH), which is a benign condition.

Therefore, repeat testing is necessary at the age of 2-3 months when the level of fetal hemoglobin has decreased using hemoglobin electrophoresis. **A Sickle cell screen (hemoglobin solubility) is not helpful in evaluating infants with possible sickle cell related conditions**. Family studies may also be helpful in distinguishing between the above conditions but must be approached with caution because of the possibility of revealing non-paternity. (See table 1)

Newborn screening will also identify:

1. Sickle cell trait and hemoglobin C and D trait – clinically benign but genetically significant carrier states associated with sickle cell disease. It will not identify beta – thalassemia trait.

2. Hemoglobin C disease and C thalassemia, mild forms of hemolytic anemia, which are of minor clinical significance and do not require early intervention.

3. Hemoglobin E trait, Hemoglobin E disease and E thalassemia (see chart).

4. Hemoglobin D disease and D thalassemia (see chart)

5. The presence of other hemoglobin variants. Identification of the specific variant in the newborn period is not possible with the current methodology

Note: If an increased amount of adult hemoglobin for birth weight is noted, the infant is presumed to have been transfused. A repeat newborn screening specimen is needed at least three months after the last transfusion when the transfused blood should no longer be present if there is no valid hemoglobin result in the infants record.

COMMENT

The purpose of the newborn hemoglobinopathy-screening program is to identify infants with SICKLE CELL related conditions. Therefore, initial test results that identify sickle hemoglobin or a hemoglobin that could in conjunction with sickle hemoglobin result in a disease, are designated as positive and followed up through the Sickle Cell Disease Center of America (SCDAA), Michigan Chapter. The responsibility for the follow-up of infants found to have non sickle cell related hemoglobinopathies, will be left to the discretion of the physician of record.

Table 1 **Possible Outcomes with Initial Test Result of FS**

DIAGNOSIS	REPEAT TEST	CBC	FAMILY STUDIES
Sickle Cell Anemia Hemoglobin SS disease	FS or SF	Low Hemoglobin	Both parents AS
Sickle Beta Thalassemia Zero	FS or SF	Low Hemoglobin Low MCV Possible sickle cells on peripheral smear	One parent AS One parent AA with elevated HB A2
Sickle Beta Thalassemia Plus	FSA, SFA or SAF	Low MCV Normal Hemoglobin	Same as Sickle Beta Thal Zero
Sickle Cell with HPFH	FS or SF	Normal	One parent AS One parent AF with Hgb F 20-30%

REPORTING TABLE

The following table includes the most commonly reported hemoglobin results
Note: Hemoglobins are generally reported in decreasing order of concentration
****SCDAA** - Sickle Cell Disease Association of America, Michigan Chapter

RESULT	DIAGNOSTIC POSSIBILITIES	ACTION REQUIRED
FS Fetal and sickle hemoglobin	• Sickle cell anemia • Sickle cell -β thalassemia • Sickle cell – hereditary persistence of fetal hemoglobin (See table 1)	You will be contacted by SCDAA* regarding diagnostic confirmation and recommendations for management
FSA Fetal hemoglobin, sickle hemoglobin and small amount of adult hemoglobin	• Sickle ß- thalassemia • Sickle cell trait	You will be contacted by the SCDAA* regarding diagnostic confirmation and recommendations for management
FSC Fetal hemoglobin, Sickle hemoglobin and hemoglobin C	• Hemoglobin SC disease; generally a milder form of sickle cell disease frequently confused with sickle cell trait	You will be contacted by the SCDAA* regarding diagnostic confirmation and recommendations for management
FSD Fetal hemoglobin, Sickle hemoglobin and hemoglobin D	• Hemoglobin SD disease; generally a milder form of sickle cell disease	You will be contacted by the SCDAA* regarding diagnostic confirmation and recommendations for management
FSE Fetal hemoglobin, Sickle hemoglobin and hemoglobin E	• Clinically benign but genetically significant	SCDAA* will provide genetic counseling
FSV Fetal, sickle hemoglobin and an unidentified variant	• Sickle cell anemia • Sickle cell-β thalassemia • Sickle cell –hereditary persistence of fetal hemoglobin • Hemoglobin S C Harlem • Hemoglobin S O Arab • Conditions phenotypically identical to sickle cell trait	You will be contacted by the SCDAA* for diagnostic confirmation and recommendations for management

REPORTING TABLE

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RESULT	DIAGNOSTIC POSSIBILITIES	ACTION REQUIRED
FAS Fetal, normal adult and sickle hemoglobin	• Sickle cell trait; which is clinically benign but genetically significant	The SCDAA* will provide genetic counseling
FAC Fetal, normal adult and hemoglobin C	• Hemoglobin C trait; which is clinically benign but genetically significant	The SCDAA* will provide genetic counseling
FAD Fetal, normal adult and hemoglobin D	• Hemoglobin D trait; which is clinically benign but genetically significant	The SCDAA* will provide genetic counseling
FAE Fetal, normal adult and hemoglobin E	• Hemoglobin E trait; which is clinically benign but genetically significant because of the possibility of offspring with Hemoglobin E Thalassemia	Genetic counseling to be provided at the discretion of the physician of record
FAV Fetal, normal adult and an unidentified hemoglobin variant	▪ Most likely clinically insignificant hemoglobin variant ▪ Hemoglobin Bart's, which is of genetic significance to children of Southeast Asian ancestry (See table 2)	Left to the discretion of the physician of record
FV Fetal and unidentified variant hemoglobin; Normal adult hemoglobin not detected	▪ Most likely clinically insignificant hemoglobin variant ▪ Hemoglobin Bart's, which is of genetic significance to children of Southeast Asian ancestry (see table 2)	Left to the discretion of the physician of record
Low A Fetal hemoglobin and an unusually low level of adult hemoglobin	▪ Possible beta thalassemia major	Physician of record responsible for repeat test and referral to pediatric hematologist for further evaluation and treatment if indicated.

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RESULT	DIAGNOSTIC POSSIBILITIES	ACTION REQUIRED
FC Fetal hemoglobin and hemoglobin C	• Hemoglobin C disease; Usually a mild form of hemolytic anemia with no need for intervention in the newborn period. • Hemoglobin C thalassemia	The SCDAA* will provide genetic counseling and disease education
FCA Fetal hemoglobin, hemoglobin C and small amount of adult hemoglobin	▪ Hemoglobin C thalassemia Usually a mild form of hemolytic anemia with no need for intervention in the newborn period ▪ Hemoglobin C trait	You will be contacted by the SCDAA* for diagnostic confirmation
FCV Fetal hemoglobin, hemoglobin C and unidentified hemoglobin variant	• Hemoglobin C Disease • Hemoglobin C Thalassemia • Conditions phenotypically identical to hemoglobin C trait	You will be contacted by the SCDAA* for diagnostic confirmation
FD Fetal hemoglobin and hemoglobin D;	▪ Homozygous hemoglobin D; a benign condition ▪ Hemoglobin D thalassemia	The SCDAA* will provide genetic counseling
FDA Fetal hemoglobin, Hemoglobin D and a small amount of adult hemoglobin	▪ Hemoglobin D thalassemia, a benign condition ▪ Hemoglobin D trait	You will be contacted by the SCDAA* for diagnostic confirmation
FDV Fetal Hemoglobin, Hemoglobin D and unidentified hemoglobin variant	▪ Hemoglobin D Disease a benign condition ▪ Hemoglobin D thalassemia ▪ Conditions phenotypically identical to hemoglobin D trait	You will be contacted by the SCDAA* for diagnostic confirmation
FE Fetal hemoglobin and hemoglobin E	▪ Hemoglobin E disease; a mild form of hemolytic anemia. ▪ Hemoglobin E thalassemia; a more severe form of hemolytic anemia causing transfusion dependence	Physician of record responsible for confirmatory testing and referral to Pediatric Hematologist

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The following table includes the most commonly reported hemoglobin results
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RESULT	DIAGNOSTIC POSSIBILITIES	ACTION REQUIRED
FEA Fetal, hemoglobin E, and a small amount of adult hemoglobin detected	▪ Hemoglobin E thalassemia; a more severe form of hemolytic anemia causing transfusion dependence ▪ Hemoglobin E trait	Physician of record responsible for confirmatory testing and referral to Pediatric Hematologist if indicated
FEV Fetal hemoglobin, hemoglobin E, and unidentified hemoglobin variant	▪ Hemoglobin E disease ▪ Hemoglobin E thalassemia ▪ Conditions phenotypically identical to hemoglobin E trait	Physician of record responsible for confirmatory testing and referral to Pediatric Hematologist if indicated

Comment on hemoglobin variants reported as "V"

The methodology used by the MDCH Laboratory will not be helpful in definitive identification of these hemoglobins. With the exception of Bart's Hemoglobin, these unidentified hemoglobins invariably have no or minimal clinical or genetic significance and could create unnecessary parental anxiety. Therefore, we only report to parents the results for which the mandatory testing law was established i.e., the sickle related conditions

Comment on Bart's Hemoglobin

Bart's hemoglobin appears in cord blood when there is a deletion of one or more of the 4 alpha goblin genes. The amount of Bart's hemoglobin reflects the number of genes that are deleted.
The presence of 1-6% Bart's hemoglobin indicates the deletion of one or two genes. This degree of deletion is clinically insignificant to the infant but may be of genetic significance. The infant may be at risk for having a child with Hydrops Fetalis, if his/her partner carries a similar deletion. This would be much more likely in an infant of Southeast Asian ancestry.

The presence of approximately 20% Bart's Hemoglobin indicates the deletion of 3 genes and the presence of hemoglobin H disease, which is characterized by mild anemia. This condition would generally be diagnosed during routine pediatric care and does not require early intervention.

Table 2 **Clinical Forms of α - Thalassemia**

# α - loci Deleted	Clinical Features	Erythrocyte Abnormalities	% Bart's
1	None	None or slight hypochromia, slight microcytosis	Newborn 1-3% > 1 yr of age - none
2	Mild Anemia	Slight hypochromia, slight microcytosis	Newborn 3-6% > 1 yr of age - none
3	Moderate to severe anemia (Hgb H disease) icterus, splenomegaly	Moderate hypochromia microcytosis, targets, polychromasia reticulocytosis	Newborn 5-20% > 1 yr of age 5-20% (Also ↑ Hgb F)
4	Fetal death with Hydrops Fetalis	Extreme microcytosis, hypochromia, and poikilocytosis	100%